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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,689	06/29/2007	Ryan Smith Westberry	186257/US	9609

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
02/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,689	WESTBERRY ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/11/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on December 5, 2008.

Preliminary Remark

Claims 15-18 are canceled.

Claims 19-23 are new.

Claims 1-14 and 19-23 are pending and are under prosecution herein.

Information Disclosure Statement

The IDS received on December 11, 2008 with fee submission (fee under 1.17p) is proper and is being considered by the Examiner.

Applicants reference that the IDS is filed under 35 CFR 1.97(e)(1), but fails to state that the information contained in the IDS was first cited in any communication from a foreign patent office in a counterpart foreign application ***not more than three months prior to the filing of the information disclosure statement***.

Therefore, the submission is proper under the fee submission in accordance with 37 CFR 1.17(p).

Drawings

The drawings received on December 5, 2008 are acceptable.

However, Figures 5A and 5B fails to comply with the sequence rules set forth in 37 CFR 1.821-1.825.

Applicants must submit: a) a paper copy of a sequence listing; b) a computer readable format (CRF) of the sequence listing; c) a statement regarding the identical nature of the paper copy of

sequence listing and its CRF version; and d) amendment to the specification to identify the nucleotide sequences disclosed in Figures 5A and 5B in the Brief description of drawings section.

A fully responsive response must comply with the requirements.

Claim Objections

The objection of claim 4 for minor informalities noted in the Office Action mailed on September 5, 2008 is withdrawn in view of the Amendment received on December 11, 2008.

The objection of claims 13 and 14 for being improper multiple dependent claim is overcome by Applicants' Amendment received on December 11, 2008. Any rejections necessitated for claims 13 and 14 are now necessitated by Applicants' amendment.

Claim Rejections - 35 USC § 112

The rejection of claims 5 and 6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on September 5, 2008 is withdrawn in view of the Amendment received on December 11, 2008.

The scope of enablement rejection of claims 11 and 12 under 35 U.S.C. 112, first paragraph, made in the Office Action mailed on September 5, 2008 is withdrawn in view of the Amendment received on December 11, 2008.

Claim Rejections - 35 USC § 102

The rejection of claims 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Monforte et al. (U.S. Patent No. 5,830,655, issued November 3, 1998), made in the Office Action mailed on

September 5, 2008 is withdrawn in view of the Amendment received on December 11, 2008, canceling the rejected claims.

The rejection of claims 1-4 and 7-12 under 35 U.S.C. 102(b) as being anticipated by Fraiser et al. (U.S. Patent No. 5,536,649, issued July 16, 1996), made in the Office Action mailed on September 5, 2008 is withdrawn in view of the Amendment received on December 11, 2008, amending the claims to require a primer comprising at least one uracil base incorporated therein.

Claim Rejections - 35 USC § 103

The rejection of claims 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fraiser et al. (U.S. Patent No. 5,536,649, issued July 16, 1996) in view of Haberhausen et al. (U.S. Patent No. 6,248,522 B1, issued June 19, 2001), made in the Office Action mailed on September 5, 2008 is withdrawn in view of the Amendment received on December 11, 2008, canceling the rejected claims.

The rejection of claims 5, 6, and 15-18 under 35 U.S.C. 103(a) as being unpatentable over Fraiser et al. (U.S. Patent No. 5,536,649, issued July 16, 1996) in view of Haberhausen et al. (U.S. Patent No. 6,248,522 B1, issued June 19, 2001), made in the Office Action mailed on September 5, 2008 is withdrawn in view of reapplication of the rejection along with claims 1-4 and 7-12.

Rejections, New Grounds - Necessitated by IDS

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danielsen et al. (WO 02/090536 A2, published November 14, 2002; IDS ref) in view of Haberhausen et al. (U.S. Patent No. 6,248,522 B1, issued June 19, 2001).

Danielson et al. disclose a reaction mixture comprising each conventional nucleotide dATP, dCTP, dGTP, and dTTP in combination with dUTP as a replacement for a portion of the dTTP, wherein said dUTP replaces about 25% of said dTTP in said reaction mixture (page 27, lines 1-2, "200 µM of dTTP and 50 µM of dUTP) and a range of 10% to 80% substitution (page 22, lines 14-15, in the phrase, "the nucleotide dUTP is used and the dUTP/dTTP ratio is about … 0.1 – 0.8.").

Regarding claim 4, Danielson et al. also contemplate said reaction mixture comprising unconventional nucleotides, such as dITP, 3-methyl-dATP, 7-methyl-dATP, 7-methyl-dGTP (page 22, lines 5-8).

With regard to claim 7 and 8, the concentration of dUTP does not exceed of about 300 µM or 100 µM (see page 27, lines 1-2 wherein dUTP has the concentration of 50 µM).

With regard to claim 9, a polymerase enzyme is employed (page 18, lines 15-20).

With regard to claim 10, the Danielson et al. employ other buffers in their amplification reaction (page 27, lines 1-2, in the phrase, "suppliers buffer.").

With regard to claim 11, the artisans employ their composition in an amplification reaction (page 27, lines 1-4).

With regard to claim 12, the artisans employ their composition in an amplification only as a first part of the reaction (page 27, lines 1-5).[1]

[1] It is clear that the first amplification reaction of Danielson et al. do not employ UDG, but only PCR with dNTPs and dUTP in the presence of a polymerase. Only after this reaction is finished, does the amplified product become purified in a column and eluted to a buffer which comprise UDG. Since claim 12 is drawn to a method of amplifying a target nucleic acid wherein UDG is not present, Danielson et al.'s first amplification reaction clearly meet the limitation.

Haberhausen et al. disclose a mixture comprising dNTPs and dUTPs and primers comprising one or more uracil bases therein, a method of amplifying a target nucleic acid, wherein said method comprises the step of amplifying the target nucleic acids with, "U-containing primer," (column 3, line 42), and dNTP mixtures comprising dATP, dCTP, dGTP, dTTP, and dUTP (column 3, lines 40-44):

"For this dUTP or U-containing primer is used in the amplification reaction instead or in addition to the normal dTTP..." (column 3, lines 40-44, Haberhausen et al.).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Danielson et al. with the teachings of Haberhausen et al., thereby arriving at the claimed invention for the following reasons.

The invention of Danielson et al. is directed to producing recombined polynucleotides by utilizing nucleotides or nucleotide analogs not normally present in naturally occurring polynucleotides, wherein, the sugar-base bonds are cleavable, or from which the base-moiety can be cleaved, thus generating so-called AP-sites. (page 2).

In performing their invention, Danielson et al. employ primers for amplifying a target nucleic acid region, wherein the amplification reaction involves the presence of dUTPs along with other conventional nucleotide analogs (see above).

Danielson et al. are not explicit in stating all possible ways in which UTPs can be employed in generating their amplified product prior to their random-cleavage:

> "For providing e.g., DNA polynucleotides comprising uracil, the starting polynucleotide is mixed with an appropriate DNA polymerase, dATP, dCTP, dGTP, dTTP, and dUTP, a suitable buffer and a pair of primers that will allow amplification of the region of interest." (page 18, lines 15-18, Danielson et al.)

However, one of ordinary skill in the art would have recognized that primers which also comprise UTP substitutions would have resulted in generating amplified products which would produce random sized-polynucleotide fragments for use in shuffling procedures.

Said one of ordinary skill in the art would have clearly recognized that such would have worked, since Danielson et al. employ UDG process (subsequent to the amplification process) for cleavage, the same enzyme of which is employed by Haberhausen et al. who generate amplified products employing primers comprising UTP substitutions as well as dUTPs incorporated throughout the amplified products.

Therefore, the invention as claimed is deemed *prima facie* obvious over the cited references.

Claims 13, 14, and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danielsen et al. (WO 02/090536 A2, published November 14, 2002; IDS ref) in view of Haberhausen et al. (U.S. Patent No. 6,248,522 B1, issued June 19, 2001) as applied to claims 1-12 above, and further in view of McLaughlin et al. (U.S. Patent No. 6,783,940 B2, issued August 31, 2004, filed October 31, 2001).

The teachings of Danielson et al. and Haberhausen et al. have already been discussed above.

Neither Danielson et al. nor Haberhausen et al. disclose that their composition/method comprise/employ sorbitol or mannitol.

McLaughlin et al. disclose that sorbitol reduces non-specific amplification in a DNA polymerase chain reaction involving sorbitol (column 2, lines 13-15), with said sorbitol concentration ranging from 0..25M to 0.35M (which is 250 mM to 350 mM, respectively; column 2, lines 25-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Danielson et al. and Haberhausen et al., with the teachings of McLaughlin et al., thereby arriving at the claimed invention for the following reasons.

Danielson et al. while are not explicit in stating that initial amplification reaction should be specific, do imply that such may be necessary:

> "The term 'a primer directed to a sequence means that the primer (preferably to be used in a PCR reaction) is designed to exhibit at least 80% degree of sequence identity to the sequence fragment of interest, more preferably, *at least 90%* degree of sequence identity to the sequence fragment of interest ... The primer is designed to ***specifically*** anneal at the sequence fragment or region ***it is directed towards at a given temperature***." (page 4, lines 29-34; Danielson et al.)

> "A template polynucleotide containing one or more AP-site(s) in unknown positions will during an amplification reaction such as PCR or a primer extension, using a plurality of ***specific***, semi-random, or random primers, give rise to the formation of a population of randomly sized polynucleotide fragments." (page 17, lines 17-19; Danielson et al.)

Thus, one of ordinary skill in the art would have been motivated to employ art-recognized means of generating specific amplicons in a PCR reaction.

In *KSR International Co. v. Teleflex Inc. (KSR)*, (citation omitted), the Supreme Court expressed that, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predicable results." *Id.* at __, 82 USPQ2d at 1395.

Clearly, one of ordinary skill in the art at the time the invention was made would have recognized that adding art-recognized amounts of sorbitol in an amplification reaction mixture, as evidenced by McLaughlin et al., would have resulted in the predictable result of providing higher specificity in amplification reaction.

Additionally, the MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success.

To this end, McLaughlin state the following:

"Other dNTPs, such as deoxyuridine triphosphate ("dUTP"), and dNTP analogs, and conjugated dNTPs may also be used..." (column 6, lines 19-22; McLaughlin et al.)

"Deoxynucleotide triphosphates ("dNTPs"), which are the building blocks of the amplification nucleic acid molecules, are typically supplied in standard PCR reactions at a concentration of 40-200 μM each ..." (column 6, lines 14-17) with contemplation of, "higher than 200 μM…" being advantageous (column 6, lines 25-26; McLaughlin et al.)

Provided that McLaughlin et al. explicitly state that the reagents employed by Danielson et al. Haberhausen et al. (dNTPs (including dUTPs in PCR reactions) are combinable and workable at the same ranges (40-200 μM each, and higher than 200 μM), one of ordinary skill in the art would have had no doubt that the combination of the teaching would have been successful.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on December 11, 2008 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on

the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 9:00 a.m. to 5:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like

assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
2/26/2009

/YJK/